Summary Basis for Regulatory Action

Date: December 10, 2014

From: Bharat Khurana, D.V.M., Ph.D., M.B.A., Chair of the Review Committee

BLA/ STN: 103914/5733

Applicant Name: Sanofi Pasteur Inc.

Date of Submission: February 13, 2014

Proprietary Name/Established Name: Fluzone® Intradermal Quadrivalent/Influenza Vaccine, Intradermal

Indication: Fluzone Intradermal Quadrivalent is an inactivated quadrivalent influenza virus vaccine indicated for active immunization of persons 18 through 64 years of age for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine.

Recommended Action: Approval

Signatory Authorities Action: Approval

Offices Signatory Authority: Wellington Sun, M.D., Director, DVRPA

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

Specific Documentation used in Developing the SBRA	Reviewer Name – Document Date
Clinical Review	Roshan Ramanathan, M.D., M.P.H. – 12/10/2014
Pharmacovigilance Review	David Menschik, M.D. – 7/29/2014
Clinical Statistical Review	Zhong Gao, Ph.D. – 11/6/2014
Assay Statistical Review	Zhong Gao, Ph.D. – 10/27/2014
CMC/Product Review	Vladimir Lugovtsev, D.V.M., Ph.D. – 12/04/2014
CMC/Facility	LCDR Donald Ertel, MT(ASCP) – 11/14/2014
CMC/Potency Test	Manju Joshi, Ph.D. – 10/30/2014
CMC/Analytical Methods & Lot Release Protocol/Quality Control	Manju Joshi, Ph.D., Alfred Del-Grosso, Ph.D. Josephine Wulu, Josephine Resnick, Karen Campbell, and Cheryl Hulme – 10/30/2014
Bioresearch Monitoring Review	Dennis Cato – 11/3/2014
Proprietary Name/Labeling Reviews	Roshan Ramanathan, M.D., M.P.H. – 12/10/2014, CDR Sonny Saini, Pharm.D., M.B.A. – 9/12/2014, Bharat Khurana, D.V.M., Ph.D., M.B.A., and Daphne Stewart

Cross referenced applications: BL103914/5240 for Fluzone High-Dose, BL103914/5369 for Fluzone Intradermal, and IND 15126, "Influenza Virus Quadrivalent [A(H1N1)/A(H3N2)/B(Yamagata)/B(Victoria); split virus; embryonated hen's eggs] Vaccine, Inactivated, Intradermal."

1. INTRODUCTION

On February 13, 2014, Sanofi Pasteur Inc. (US License 1725) submitted a supplement to their Biologics License Application (BLA) for Fluzone Intradermal Quadrivalent (proprietary name), a quadrivalent formulation of influenza vaccine to be administered intradermally. This formulation contains 9 µg hemagglutinin (HA) antigen of each of the four virus strains (one H1N1, one H3N2, and two B strains: one each from the Yamagata and Victoria lineages), for a total of 36 µg of HA antigen per 0.1 mL dose. Fluzone Intradermal Quadrivalent formulation is supplied in a single-dose, prefilled 0.1 mL microinjection system.

In this BLA supplement (sBLA), the applicant submitted clinical data to demonstrate a similar safety profile and non-inferior immunogenicity of Fluzone Intradermal Quadrivalent compared to Fluzone Intradermal vaccine (for each of the four strains in common) and to establish that the presence of second B strain did not interfere with immune responses elicited by the other B strain or the two A strains. In addition, Sanofi Pasteur submitted information on manufacturing facilities, equipment and processes to provide data demonstrating that the manufacturing process is similar to that of current licensed Fluzone High-Dose or Fluzone Intradermal vaccine formulations.

2. BACKGROUND

Influenza, a respiratory and systemic illness caused by influenza virus infection, is an important cause of infectious morbidity and mortality worldwide. Humans are primarily affected by two influenza virus types, A and B. Since 2001, two influenza B lineages have co-circulated during each influenza season in the United States, usually with one lineage predominating over the other in most seasons. Public health agencies have only been able to predict the prevailing B lineage roughly half the time. For this reason, previous meetings of the Vaccine Related Biological Products Advisory Committee (VRBPAC) have discussed the need for quadrivalent influenza vaccines to eliminate the risk that the incorrect B lineage is selected for inclusion in the vaccine.

Sanofi Pasteur currently has one quadrivalent influenza vaccine formulation (Fluzone Quadrivalent) and three trivalent influenza vaccine formulations (Fluzone, Fluzone High-Dose and Fluzone Intradermal) licensed in US under BL 103914. All these influenza vaccine formulations share similar manufacturing process and have overlapping compositions. *Fluzone,* containing 30 µg hemagglutinin (HA) per strain (A/H1N1, A/H3N2, and B) per mL, for a total of 90 µg HA per mL and 0.25 or 0.5mL/dose, is indicated for active immunization of persons 6 months of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. *Fluzone High-Dose,* containing 120 µg HA/strain/mL and 0.5mL/dose, is indicated for active immunization of persons 65 years of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. *Fluzone Intradermal,* containing 90 µg HA/strain/mL and 0.1mL/dose, is indicated for active immunization of adults 18 through 64 years of age against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.

Sanofi Pasteur's quadrivalent influenza vaccine formulation, *Fluzone Quadrivalent*, is an extension of the trivalent Fluzone vaccine used for the prevention of influenza disease in individuals 6 months of age and older and contains 30 µg HA/strain (two influenza A strains and two influenza B strains)/mL, for a total of 120 µg HA/mL and 0.5 mL/dose. The *Fluzone Intradermal Quadrivalent*, which was reviewed in this efficacy supplement, is an extension of the trivalent Fluzone Intradermal vaccine used for the prevention of influenza disease in adults 18 through 64 years of age. Fluzone Intradermal Quadrivalent contains 90 µg HA/strain (two influenza A strains and two influenza B strains)/mL, for a total of 36 µg HA per 0.1 mL dose. By adding a second type B strain of an alternate lineage to the trivalent influenza vaccine containing A/H1N1, A/H3N2 strain and one B strain, the resulting quadrivalent vaccines are expected to provide broader protection against the influenza virus strains circulating during a particular epidemic season. The two B strains in the Fluzone Intradermal Quadrivalent represent one strain of each of the two co-circulating influenza B lineages, B/Yamagata-like and B/Victoria-like.

The safety and immunogenicity of Fluzone Intradermal Quadrivalent were evaluated in one clinical study, Study QID01, in adults 18 through 64 years of age.

3. CHEMISTRY, MANUFACTURING, AND CONTROL INFORMATION

The Fluzone Intradermal Quadrivalent vaccine for intradermal use, is a sterile suspension of the four strains (one H1N1, one H3N2, and two B strains: one each from the Yamagata and Victoria lineages) prepared from influenza viruses propagated in embryonated chicken eggs. Antibiotics are not used in the manufacture of Fluzone Intradermal Quadrivalent vaccine. Fluzone Intradermal Quadrivalent vaccine does not contain the preservative thimerosal (mercury derivative) and no gelatin is added to the vaccine. Fluzone Intradermal Quadrivalent will be supplied at 0.1 mL volume in a single dose pre-filled -----(b)(4)---- Microinjection System (MIS).

The only major CMC issue encountered and brought to resolution during the review process is summarized below:

> Sanofi Pasteur had initially requested a Triton X-100 specification of ----(b)(4)---- in the Fluzone Intradermal Quadrivalent drug product because of the inclusion of additional antigen, representing the 4th influenza virus strain, to formulate the drug product. The proposed Triton X-100 specification of Fluzone Intradermal Quadrivalent drug product was an increase from ≤ 50 µg/0.1 mL dose, as in case of trivalent Fluzone Intradermal vaccine, to --------(b)(4)-------- dose. We noticed that the Triton X-100 concentration in the three consistency lots ----------(b)(4)----------, respectively, and that the drug product lot used in the clinical trial had a Triton X-100 concentration of 509.9 µg/mL. Since the information provided in the original submission was not sufficient to address the potential impact of the increased Triton X-100 concentration on immunogenicity and safety of the Fluzone Intradermal Quadrivalent vaccine, Sanofi Pasteur was asked to provide additional data to support the increased specification of Triton X-100. Sanofi Pasteur admitted that, at this time, it does not have additional preclinical or clinical immunogenicity data to support the proposed ------(b)(4)----- Triton X-100 drug product specification. Sanofi Pasteur, however, explained that due to assay variability (validated intermediate precision of the Triton X-100 method of

quantitation; Validation Report Q_0518386) the result 509.9 µg/mL obtained for the clinical lot could be as high as 548 µg/mL. Based on the manufacturing consistency range (-----(b)(4)----- µg/mL), the use of these material in the clinical study and the assay variability, Sanofi Pasteur proposed a new Triton X-100 specification of ≤ 550 µg/mL or ≤ 55 µg/0.1 mL dose.

Based on the information provided by the manufacturer, the revised Triton X-100 specification of ≤ 550 µg/mL or ≤ 55 µg/0.1 mL dose of Fluzone Intradermal Quadrivalent vaccine is acceptable. The new specification for Triton X-100 in Fluzone Intradermal Quadrivalent formulation represents a 10% increase in comparison to that in the currently licensed Fluzone Intradermal formulation (≤ 500 µg/mL or ≤ 50 µg/0.1 mL dose). The composition of Fluzone Intradermal Quadrivalent vaccine is listed in the table below.

Composition of Fluzone Intradermal Quadrivalent Vaccine

Ingredient	**Quantity (per 0.1 mL dose)**	**Function**
Split influenza virus, inactivated strains[a]:	36 µg HA total	Active substance
A (H1N1)	9 µg HA	Active substance
A (H3N2)	9 µg HA	Active substance
B (Victoria lineage)	9 µg HA	Active substance
B (Yamagata lineage)	9 µg HA	Active substance
Sodium phosphate-buffered isotonic sodium chloride solution	QS[b] to appropriate volume	Diluent
Formaldehyde	≤20 µg	Residual
Octylphenol Ethoxylate (Triton X-100)	≤55 µg	Residual

[a]per United States Public Health Service (USPHS) requirement
[b]Quantity Sufficient

Drug Substance

The manufacturing operation uses embryonated chicken eggs to produce monovalent ------(b)(4)------. The virus is harvested from the allantoic fluid, inactivated with formaldehyde, concentrated, purified in a linear sucrose density gradient solution using a continuous flow centrifuge, and finally chemically disrupted using a non-ionic surfactant, octylphenol ethoxylate (Triton® X-100) to produce a "split virus". The split-virus is then further purified by ultrafiltration and diluted to appropriate hemagglutinin (HA) concentration with sodium phosphate-buffered isotonic sodium chloride solution. ----------(b)(4)----------, are used to formulate the bulk.

The drug substance for Fluzone Intradermal Quadrivalent (QIV-ID) utilizes the similar manufacturing process, controls and release testing as Fluzone High-Dose (licensed on December 23, 2009 as a supplement to Fluzone under BLA 103914/5240) or Fluzone Intradermal (licensed on May 9, 2011 as a supplement to Fluzone under BLA 103914/5369) with some minor changes that were made to accommodate increased antigen concentration and improve product robustness. These changes include:

- ----------(b)(4)----------
- ----------(b)(4)----------
- ----------(b)(4)----------

The descriptions of manufacturing process and process controls, analytical procedures and specifications, batch analyses and stability data of monovalent lots were provided in the BLA supplement. The stability results support ----------(b)(4)----------.

Drug Product

The Fluzone Intradermal Quadrivalent drug product is formulated by combining monovalent -----(b)(4)------ of the four strains of influenza identified for the upcoming influenza season (one H1N1, one H3N2, and two B strains: one each from the Yamagata and Victoria lineages) at 90 µg HA/mL/strain, and ----------(b)(4)----------. The final drug product is then sterile filtered and filled into the final container, assembled and labeled. The drug product is manufactured at the Sanofi Pasteur Inc. facility located in Swiftwater, PA and filled, labeled and packaged at the Sanofi ----(b)(4)----

Manufacture of Fluzone Intradermal Quadrivalent drug product utilizes the current formulation and filling processes, which are licensed for Fluzone Intradermal drug product. Formulation of the bulk product includes the addition of a fourth strain (B Strain) and minor changes in the --------(b)(4)-------- attributes to improve product robustness. These changes include an --(b)(4)--

Additionally, the specification of Triton X-100 in the (b)(4) was increased from ----(b)(4)---- (in Fluzone Intradermal) to -----(b)(4)----. The higher ---(b)(4)-- Triton X-100 specification is ----------(b)(4)----------.
Correspondingly, the increase in antigen concentration is accompanied by an increased Triton X-100 concentration in the DS manufacturing process and therefore assures consistent overall composition.

The bulk product is ----------(b)(4)----------

----------(b)(4)---------- until time of filling. The final drug product is filled into the -(b)(4)- ---------- Microinjection System -----(b)(4)-----.

Process Validation
The formulation and filling process for Fluzone Intradermal Quadrivalent utilizes process parameters which were previously validated for the currently licensed Fluzone Intradermal process and performed in the same formulation facility (----------(b)(4)--------, Swiftwater, PA) ----------(b)(4)----------, respectively. Therefore, only consistency was verified.

The formulation process validation for Final Bulk Product included Formulation Consistency Lot Validation and Formulation Aseptic Process Simulation at ----------(b)(4)--------. Process parameters used during the bulk product formulations were ----------(b)(4)---------- ----------. The validation study was executed using three consecutively manufactured lots of Fluzone Intradermal Quadrivalent Final Bulk Product. The validated batch size of Final Bulk Product is -(b)(4)-.

The consistency lot validation study included the filling of Fluzone Intradermal Quadrivalent syringes at the Sanofi ----------(b)(4)----------. The process validation for Filled Product included Filling Consistency Lot Validation and Aseptic Process Simulation. The process parameters identified for the final product presentation were ----------(b)(4)---------- ----------. In addition to the process parameters, each batch was tested according to the Critical Quality Attributes, such as, ----------(b)(4)---------- ----------. The validation study was executed using three batches of Fluzone Intradermal Quadrivalent Filled Product

Results of the completed consistency validation studies demonstrated that the manufacturing process can consistently yield drug product that is suitable for its intended purpose.

Control of Excipients
The excipients used in the manufacture of Fluzone Intradermal Quadrivalent drug product are: Sodium Chloride, Sodium Phosphate ----(b)(4)---- Sodium Phosphate --(b)(4)--. Since all of the analytical procedures and specifications applied for release of the excipients used during the manufacture of drug product are identical to those used for Fluzone and comply with the -(b)(4)- ----------, validation was not performed.

Specifications
The batch release acceptance criteria for the Drug Product are given in the following tables:

Acceptance Criteria for the Fluzone Intradermal Quadrivalent Drug Product, **Final Bulk**

Test	Acceptance Criteria
Sterility	No Growth
---------(b)(4)--------	----------(b)(4)----------
----------(b)(4)---------- ----------	----------(b)(4)----------
----------(b)(4)----------	----------(b)(4)----------
------(b)(4)------	----------(b)(4)----------
----------(b)(4)----------	----------(b)(4)--
(b)(4)	-(b)(4)-

Acceptance Criteria for the Fluzone Intradermal Quadrivalent Drug Product, **Unlabeled Filled Product**

Test	Acceptance Criteria
Sterility	No Growth
Major A Defects	------(b)(4)------- ---------- ----------

Acceptance Criteria for the Fluzone Intradermal Quadrivalent Drug Product, **Labeled Filled Product**

Test	Acceptance Criteria
Volume Check	Not Less Than (NLT) 0.10 mL/syringe
Major B Defects	--------(b)(4)---------- ----------
Final Identity by -------(b)(4)-------	Identifies as influenza strains

Container Closure

The final drug product is filled into the ----------(b)(4)---------- Microinjection System (hereafter referred to as ----(b)(4)---). This container closure system (---(b)(4)---) for Fluzone Intradermal Quadrivalent Vaccine ----------(b)(4)---------- ----------. The ---(b)(4)--- is a modified ---(b)(4)--- glass syringe configured with a nominal volume of 0.5 mL, 30-gauge affixed stainless steel 1.5 mm intradermal needle, with an external non-fluid path needle shielding system that incorporates a needle cover that extends over the needle after completion of the injection. ----(b)(4)---- is primary packaging (container closure system) with a delivery function, and is prefilled with 0.1 ml Fluzone Intradermal Quadrivalent Vaccine for intradermal administration.

Stability

Stability studies were initiated to evaluate the drug product, Fluzone Intradermal Quadrivalent while stored as Final Bulk Product, and as Filled Product.

----------(b)(4)----------

A long-term stability study for Filled Product was performed on three batches of Filled Product. The Filled Product stability study was completed to the (b)(4) month time point for one batch and to 9 months for two batches. All results comply with the acceptance criteria for Physical

Examination, (b)(4) SRID (potency), Sterility, Closed Container Integrity Testing (CCIT), Volume and Major B Defects. Based on the testing results obtained from the stability study, the shelf life of Fluzone Intradermal Quadrivalent Drug Product is 9 months at 2°C to 8°C when filled into ----------(b)(4)---------- Microinjection System.

For post-licensure stability studies, three batches of each drug product (final bulk product and filled container) will be tested ---(b)(4)--- to confirm the expiration period.

CBER Lot Release

The lot release protocol (LRP) template for Fluzone Intradermal Quadrivalent Vaccine is the same as the one currently in use by Sanofi for other Fluzone products except that it is amended to add the specifications for the Fluzone Intradermal Quadrivalent Vaccine. The specification for Triton X-100 content was finalized and a revised LRP submitted in amendment 103914/5733/5006 to reflect the final specification. This final LRP template was reviewed and is appropriate for use for release of Fluzone Intradermal Quadrivalent Product. In-support testing was performed to evaluate for potency by SRID assay, and all test specifications were met. This testing was carried out on expired final bulk due to lack of available unexpired product. For routine lot release, the applicant will submit samples from final bulk along with a Lot Release Protocol for review. A lot testing plan has been developed by CBER and will be used for routine lot release.

Facilities Review/Inspection

The qualification, validation, and control activities, as related to facility, equipment, and container closure appear adequate for the drug substance and drug product manufacturing of Influenza Virus Vaccine, Fluzone Intradermal Quadrivalent. From the supplement review, there appears to be no evidence that the identity, strength, safety, quality and purity of the product produced in the Swiftwater and ---(b)(4)--- facilities would be adversely impacted. The facilities involved in the manufacture of Influenza Virus Vaccine, Fluzone Intradermal Quadrivalent (QIV-ID) are listed in the table below. The activities performed and the inspectional history of the facilities is included in the table.

Table of the manufacturing facilities for Fluzone Intradermal Quadrivalent (QIV-ID)

Name/address	FEI number	DUNS number	Inspection/ waiver	Justification
Drug Substance Manufacturing and Formulation: Sanofi Pasteur Inc., 1 Discovery Drive, Swiftwater, PA 18370, United States	2518760	086723285	Inspection Waived	Team Bio May 2014 VAI See notes below
Drug Product Fill/Finish, Labeling, Testing: ----------(b)(4)----------	---(b)(4)---	---(b)(4)---	Inspection Waived	Team Bio March 2014 VAI See notes below

Justification for waiving inspections
Team Biologics performed surveillance inspections of both manufacturing facilities within the past 10 months. In both cases, all 483 issues were resolved and the inspections were both classified as voluntary action indicated (VAI).

Environmental Assessment
The Supplement included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(a). The FDA concluded that this request is justified as the manufacturing of this product will not increase the use of the active moiety and no extraordinary circumstances exist that would require an environmental assessment.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

No nonclinical pharmacology/toxicology data were provided in the supplement. For the nonclinical safety evaluation of the Fluzone Intradermal Quadrivalent vaccine, previous non clinical and clinical data obtained with licensed Fluzone vaccines were considered supportive and no additional local or repeat dose toxicity studies were conducted or considered necessary.

5. CLINICAL PHARMACOLOGY

No clinical pharmacology or pharmacokinetic studies were performed or considered necessary.

6. CLINICAL/ STATISTICAL

The sBLA included safety and immunogenicity data from a single clinical trial, QID01, a pivotal, Phase 3, randomized, double-blinded, active-controlled, multi-center trial evaluating the immunogenicity and safety of the quadrivalent influenza vaccine by intradermal route in adults 18 through 64 years of age.

Study participants were randomized 2:1:1 to receive either Fluzone Intradermal Quadrivalent, or one of the trivalent influenza vaccine formulations by intradermal route containing either the B strain from the B/Yamagata lineage (TIV-ID1) or a different B strain from the B/Victoria lineage (TIV-ID2). At enrollment, a subset of 2/3 of subjects was randomly selected to provide a pre-vaccination blood sample at day 0 and at 28 days post-vaccination. Solicited adverse reactions were collected up to 7 days post-vaccination and unsolicited adverse events (AEs) were collected up to 28 days post-vaccination. Serious adverse events (SAEs) including adverse events of special interest (AESIs) were collected throughout the trial (day 0 through 6 month follow up period.) AESIs included: new onset Guillain-Barre syndrome, Bell's palsy, encephalitis/myelitis, optic neuritis, Stevens-Johnson syndrome and toxic epidermal necrolysis.

A total of 3360 subjects were enrolled in the trial: 1676 subjects in the Fluzone Intradermal Quadrivalent group and 1684 subjects in the TIV-ID Pooled group (837 and 847 subjects in the TIV-ID1 and TIV-ID2 groups, respectively).

The primary objective was to demonstrate non-inferiority of Fluzone Intradermal Quadrivalent vaccine versus TIV-ID1, the licensed 2012-2013 Fluzone Intradermal vaccine containing the B strain from the Yamagata lineage, (B/Texas/6/2011 or B1) and TIV-ID2, the investigational vaccine containing the alternate B strain from the Victoria lineage (B/Brisbane/60/2008 or B2). Non-inferiority of Fluzone Intradermal Quadrivalent to TIV-ID in terms of hemagglutination

inhibition (HAI) geometric mean titers (GMTs) and seroconversion rates was demonstrated for the four strains at 28 days post-vaccination. For each of the four strains, the lower limit of the 2-sided 95% CI for the ratio of GMTs (Fluzone Intradermal Quadrivalent divided by pooled TIV-ID for the A strains, or the TIV-ID containing the corresponding B strain) was > 0.67 and the difference between the seroconversion rates (Fluzone Intradermal Quadrivalent minus pooled TIV-ID for the A strains, or the TIV-ID containing the corresponding B strain) was > -10%. The secondary objective was to demonstrate superiority of Fluzone Intradermal Quadrivalent against TIV-IDs for the B strain not contained in TIV-ID1 or TIV-ID2. Fluzone Intradermal Quadrivalent induced an immune response to each B strain (as assessed by HAI GMTs and seroconversion rates) that was superior to the response induced by the TIV-ID that did not contain the corresponding B strain at 28 days post-vaccination. For each B strain, the lower limit of the 2-sided 95% CI for the ratio of GMTs was > 1.5, and the lower limit of the 2-sided 95% CI for the difference between the seroconversion rates was > 10%.

The submitted data support non-inferior immunogenicity of Fluzone Intradermal Quadrivalent for each of the four strains in comparison to TIV-ID1 and TIV-ID2, and superior immunogenicity of Fluzone Intradermal Quadrivalent to each B strain in comparison to TIV-ID1 and TIV-ID2 that did not contain the corresponding B strain at 28 days post-vaccination in adults 18 through 64 years of age.

Pediatric Research Equity Act
Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), an assessment of the safety and effectiveness of the product for the claimed indication in all pediatric age groups must be submitted at the time an application for a new active ingredient, new dosage form, new dosing regimen, new indication, or new route of administration is submitted, unless the requirement for assessment has been deferred or waived. Fluzone Intradermal Quadrivalent formulation contains a new active ingredient, new dosage and new indication due to the addition of the second influenza B strain.

The pediatric development plan for Fluzone Intradermal Quadrivalent was presented to the FDA's Pediatric Review Committee on April 3, 2013. The Committee concurred with CBER's assessment and a full waiver of pediatric assessment of Fluzone Intradermal Quadrivalent was granted. The pediatric study requirement was waived for persons 0 to < 6 months of age because available data in this age group indicate that serum antibody responses to inactivated influenza vaccines are not as robust as in older children, likely due to inherent immaturity of the immune system and interference from maternal antibody. The pediatric study requirement was waived for persons 6 months through 17 years of age because the product fails to represent a meaningful therapeutic benefit over existing therapies and is not likely to be used by a substantial number of pediatric patients.

Bioresearch Monitoring Inspection
Bioresearch Monitoring inspections of three domestic clinical investigators were conducted in support of this supplement. The inspection reports did not reveal any issues that would impact the data collected and submitted in this application.

7. SAFETY

In Study QID01, information on the occurrence, intensity and duration of local and systemic adverse reactions was recorded on the day of vaccination and the subsequent 7 days for solicited

reactions and within 28 days after vaccination for unsolicited adverse events (AEs). Serious adverse events (SAEs), including Adverse Events of Special Interest (AESIs), within the28 days following vaccination and up to 6 months after vaccination were also collected.

A total of 1672 subjects received one dose of Fluzone Intradermal Quadrivalent formulation; 1683 subjects received one dose of TIV-ID in QID01; 837 subjects received one dose of TIV-ID1 and 846 subjects received one dose of TIV-ID2. The size of the safety database was considered adequate because there were no safety concerns raised by the safety data from QID01, the safety experience with Fluzone Intradermal was considered supportive of the licensure of Fluzone Intradermal Quadrivalent, and both vaccines share similar manufacturing processes and have overlapping compositions.

The percentages of subjects who reported solicited local adverse reactions within 7 days post-vaccination were slightly higher for recipients of Fluzone Intradermal Quadrivalent than for recipients of TIV-ID1 and TIV-ID2, although these reactions were mostly mild (Grade 1 and 2). The most common (occurring in ≥10%) local adverse reactions following vaccination with Fluzone Intradermal Quadrivalent vs. TIV-ID pooled groups were: pain (53.3% vs. 49.2%), pruritus (52.1% vs. 45%), erythema (36.7% vs. 33.1%), swelling (19.5% vs. 14.7%), and induration (17.0% vs. 12.4%); the most common solicited systemic adverse reactions were myalgia (34.1% vs. 30.1%), headache (33.1% vs. 32.3%), malaise (27.7% vs. 28.4%), and shivering (12.1% vs. 10.8%).

Unsolicited adverse events within 28 days of vaccination were similar among the study arms in terms of frequency and diagnosis (23.1% in the Fluzone Intradermal Quadrivalent group; 22.9% in the pooled TIV-ID groups). The most commonly reported unsolicited non-serious adverse events were cough, headache, and oropharyngeal pain.

No AE led to study discontinuation after Fluzone Intradermal Quadrivalent administration. During the 28 days following vaccination, a total of 6 (0.4%) recipients in the Fluzone Intradermal Quadrivalent group, and 5 (0.3%) recipients in the pooled TIV-ID groups. Throughout the study period (6 months post-vaccination), a total of 20 (1.2%) recipients in the Fluzone Intradermal Quadrivalent group, 14 (1.7%) recipients in the TIV-ID1 group, and 11 (1.3%) recipients in the TIV-ID2 group experienced at least one SAE. No SAEs were considered related to vaccination.

No deaths occurred within 28 days after vaccine injection. During the six-month follow-up period, one subject, a 60-year-old male, died of acute coronary myocardial infarction symptoms 177 days after Fluzone Intradermal Quadrivalent administration. The cause of the death was considered not related to vaccine administration by the Investigator.

Pharmacovigilance Plan

No safety signals were identified in the pre-licensure data. The applicant's pharmacovigilance plan, which establishes routine pharmacovigilance, was found to be acceptable.

QIV-ID clinical trials have excluded pregnant women, lactating women, and immunocompromised or immunosuppressed individuals. Sanofi Pasteur proposed to assess the safety of Fluzone Intradermal Quadrivalent vaccine administered during pregnancy through use of a pregnancy registry that would be consistent with the registry being currently used for Fluzone Quadrivalent (intramuscular vaccine) and with the 2002 FDA Guidance for Industry:

Establishing a Pregnancy Exposure Registry. Briefly, the pregnancy registry is designed to collect and analyze information on vaccine exposures, pregnancy outcomes, and fetal and offspring outcomes. Women are to be enrolled in the registry prospectively (after vaccine exposure but before the conduct of any prenatal tests that could inform pregnancy outcomes), although retrospective reports (when the condition of the fetus has already been assessed through prenatal testing) will be included and analyzed separately. Although there are several limitations in the pregnancy registry protocol, no product specific safety concerns have been identified to date that would warrant a more stringent pregnancy safety study. The planned registry was found to be acceptable by CBER.

8. ADVISORY COMMITTEE MEETING

A Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting was not required for Fluzone Intradermal Quadrivalent because of CBER's experience with the currently licensed Fluzone Intradermal and other licensed quadrivalent inactivated influenza vaccines. Moreover, Fluzone Intradermal Quadrivalent shares the same manufacturing process as Fluzone Intradermal except for the addition of a second influenza B strain. Since our review of information submitted in the supplement did not raise concerns or identify any controversial issues, which would have benefited from advisory committee discussion, it was agreed that review of this sBLA by the VRBPAC was not necessary.

9. LABELING

To be consistent with similar US-licensed quadrivalent influenza vaccines, the proprietary name Fluzone Intradermal Quadrivalent was recommended. Sanofi Pasteur Inc. agreed to use this proprietary name. The carton and syringe labels were reviewed and found to be acceptable after several minor changes. The proposed package insert (PI) required some modifications. One of the major modifications included adding a rationale to Section 8.1 (Pregnancy) of the package insert to indicate that a developmental and reproductive toxicity study performed with the trivalent formulation of *Fluzone Intradermal* was considered relevant to *Fluzone Intradermal Quadrivale*nt because both vaccines share the same manufacturing process and route of administration. As the proposed PI required several modifications, after negotiations with the applicant and many rounds of modifications following our review, the review committee found the PI for Fluzone Intradermal Quadrivalent formulation to be acceptable.

10. RECOMMENDATIONS AND RISK/BENEFIT ASSESSMENT

Recommended Regulatory Action

Based on the review of the data provided regarding safety and effectiveness, as well as information on manufacturing process, the review committee recommends approval of this sBLA for Fluzone Intradermal Quadrivalent formulation.

Risk/Benefit Assessment

Data submitted to the BLA supplement establish a substantial likelihood of benefit with respect to the effectiveness of Fluzone Intradermal Quadrivalent in adults 18 through 64 years of age: 1) non-inferiority of immune responses to QIV-ID compared to Fluzone Intradermal with respect to the four strains contained in the vaccine and 2) superiority of immune responses induced by Fluzone Intradermal Quadrivalent formulation with respect to the influenza B strain not contained in the TIV-ID comparator. Though local reactogenicity of Fluzone Intradermal Quadrivalent was slightly higher than the Fluzone Intradermal, data demonstrate that Fluzone

Intradermal Quadrivalent has a safety profile that is generally comparable to that for Fluzone Intradermal. The overall risk-benefit profile of this product was determined to be favorable since the risks of vaccination with Fluzone Intradermal Quadrivalent in adults 18 through 64 years of age and older have been found to be minimal, there is a substantial likelihood of benefit in the prevention of influenza disease caused by the four vaccine types/subtypes contained in the vaccine, and the addition of second B strain in the vaccine eliminates the risk that the incorrect B lineage is selected for inclusion in the vaccine.

The safety of Fluzone Intradermal Quadrivalent in pregnant women was not evaluated in support of this application. Sanofi Pasteur has proposed a cohort study to evaluate the safety of Fluzone Intradermal Quadrivalent in pregnant women as a post-marketing commitment. Fluzone Intradermal Quadrivalent therefore presents a favorable overall risk-benefit profile.

Post-marketing Risk Management Activities

Sanofi Pasteur Inc. agreed to establish a pregnancy registry (final protocol submission by June 30, 2015) that will enroll women exposed to Fluzone Intradermal Quadrivalent during pregnancy and collect data on their outcomes and newborn health status. The enrollment will be through at least August 30, 2019 (four years). Annual reports for this registry will be submitted with the Periodic Benefit-Risk Evaluation Report (PBRER) that includes all other Fluzone influenza vaccines. When the registry has collected data on the outcomes specified in the protocol for four years, Sanofi will submit a final study report by December 31, 2020. After submission of the registry report, Sanofi Pasteur will continue enrolling in the registry pending CBER review of the final study report and determination that the registry can be discontinued.